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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/927,436	08/13/2001	Mitra Tadayoni-Rebek	0942.5300001/RWE/AGU	6227

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EXAMINER	
LUKTON, DAVID	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 11/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/927,436	TADAYONI-REBEK ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-20 and 39-48* is/are pending in the application.

4a) Of the above claim(s) *44-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-20,39-43,48 and 49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims 16-20 and 39-48 remain pending.

Applicants' species elections (response filed 8/20/04) are acknowledged. In response to selection of a specific "marker molecule" (that is the "target" of the synthesis), applicants have elected the peptide of SEQ ID NO: 3 in which the epsilon amino groups of the lysines bear a tetramethylrhodamine group. As for the "protein" (of step (b), claim 16), applicants have chosen "MBP-95aa" in which the following group replaces the C-terminal carboxyl:

$$-CO-S-CH_2-CH_2-SO_3^-$$

Claims 44-47 are withdrawn from consideration, since they do not encompass the elected specie. Within the elected species, there is just one "label", one molecular weight, and one pI. However, applicants may, in response to this Office action, elect another specie, which is a specific mixture of labeled proteins in which each of the following parameters are defined for each protein: molecular weight, isoelectric point, and label at each position. Claims 16-20, 39-43, 48 are examined in this Office action.

✧

Claims 16-20, 39-43, 48-49 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Claim 16 is drawn to a method of preparing **a** marker molecule. There is no suggestion that one can or should obtain a mixture of two or more compounds. Claim 17, by contrast, mandates that one produce a mixture of two or more compounds. Accordingly, the claim dependence is not proper. It is suggested that claim 17 be written in independent form. Similarly, claim 20 is not subgeneric to claim 19.

- Claim 42 recites the term "about" in reference to a range, thus rendering the claim indefinite.

- Claim 48 is dependent on claim 16 (and on 19). As indicated above, claim 16 is drawn to a method of preparing **a** marker molecule. There is no suggestion that one can or should obtain a mixture of two or more compounds. Claim 48 recites that "each" molecule is labeled with the "same" label. Given that the practitioner of the claim 16 invention would produce one and only one compound, how is it possible that one could have anything but all of the molecules having the same label? Perhaps dependence on claim 17 (and 20) is intended.

- In claim 49, the term "MBP-95aa" is used, but is not defined. One option would be to add the following phrase to the claim:

  - - wherein "MBP-95aa" is a 95-amino acid peptide which is obtained by appending the tripeptide Met-Arg-Met to the C-terminus of a peptide that corresponds to residues 1-92 of the 404 amino acid *Escherichia coli* maltose binding protein. - -

  Another option would be to provide the full sequence of "MBP-95aa".

- In claim 49, the term "TMR" is used, but is not defined. If consistent with intentions, applicants could simply add the following phrase:

  - - wherein "TMR" represents tetramethylrhodamine. - -

  Another option would be to use the name of the compound in place of the abbreviation.

✧

The following is a quotation of 35 USC. §103 which forms the basis for all obviousness rejections set forth in the Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 16, 17, 19, 20, 39, 40, 42, 43 are rejected under 35 U.S.C. §103 as being unpatentable over Canne (USP 6,326,468).

Canne discloses a peptide ligation method in which a peptide bearing an N-terminal cysteine is reacted with another peptide bearing a C-terminal thioester group to form a larger peptide. Reaction schemes are summarized, e.g., in figures 1, 16, 20 and 21. As is evident, the coupling process can be performed more than once. Also suggested (col 14, line 60+) is that the "first peptide segment" or the "incoming peptide segment" can be used in excess.

The first issue here pertains to step (a) of claim 16. This step recites "labeling a molecule". However, as a practical matter, this step has little impact, in the absence of any

limitations on the term "labeling". Consider, for example, the simple compounds toluene and benzyl alcohol. One could say that benzyl alcohol is just toluene that has been "labeled" with a hydroxyl group. Or consider the amino acid alanine. One could say that this is just glycine that has been "labeled" with a methyl group. Or take the case of a dipeptide such as Phe-Glu. One could say that the dipeptide Phe-Glu is just glutamic acid that has been "labeled" with phenylalanine. The term "labeling" does not require that there be a fluorescent group, or a UV-detectable group, or a radioactive moiety. All that matters is that the presence of the group or substituent in question be detectable by some means that would be known to the analytical chemist of ordinary skill. As it happens, then, all peptides, without exception, are "labeled" molecules, regardless of their structure or sequence.

In view of the foregoing, step "b" of claims 16 and 19 is met without further explanation. The next issue concerns claims 17 and 20. In each case (claims 17 and 20), step (c) is interpreted to mean that (i) one repetition is sufficient, and (ii) the resulting mixture need not have more than two peptides. These claims (claims 17 and 20) are also interpreted to mean that the two peptides in question need not be present in equal amounts, or even anything approaching equal amounts. That being the case, the reality is that when a coupling procedure is carried out between any two peptide fragments, whether using the method of Canne, or a more conventional activated ester approach, some residual peptide is inevitably going to remain if the two peptides are used in a 1:1 stoichiometry. For example,

suppose that peptide "A" and peptide "B" are coupled together to produce peptide "A-B" using a given coupling procedure (conventional or otherwise). In such a situation, most peptide chemists would be quite satisfied if the product mixture contained peptide "A-B", starting peptide "A" and starting peptide "B" in a 99:0.5:0.5 ratio. The conditions of claims 17 and 20 would be met if three peptides were present in a 99:0.5:0.5 ratio; the conditions of claims 17 and 20 would be met if three peptides were present in a 1000:1:1 ratio. In reality, the peptide chemist of ordinary skill will tend to use one of the two peptides in excess over the other. Often it is the less "valuable" peptide that is used in excess; in other times the one that is used in excess is the one that can be most easily eliminated. This is well known to the peptide chemist of ordinary skill. But in addition, Canne makes reference to this (col 14, line 60+). Thus, suppose that the "first" peptide bears a C-terminal thioester, and the "second" peptide bears an N-terminal cysteine, and that the "second" peptide is used in 10% molar excess (relative to the first peptide). The result (of the reaction) will be a mixture of two peptides in approximately a 10:1 ratio.

Thus, the claims are rendered obvious.

✧

Claims 16, 39, 40, 42, 43 are rejected under 35 U.S.C. §103 as being unpatentable over Kent (USP 6,307,018).

Kent discloses (e.g., figure 1) a coupling procedure in which a "peptide 1" bearing a

thioester group is reacted with a "peptide 2" bearing an N-terminal sulfhydryl moiety. As indicated above (the §103 over Canne), the term "labeling" in step (a) of claim 16 is not a meaningful limitation.

Thus, the claims are rendered obvious.

✧

Claims 16, 39, 40, 42, 43 are rejected under 35 U.S.C. §103 as being unpatentable over Kent (USP 6476190)

Kent discloses (e.g., figure 1) a ligation procedure in which a C-terminal thioester of a "first" peptide is reacted with a "second" peptide, wherein the second peptide bears an N-terminal bromoacetyl group. The result is a new peptide which itself contains a thioester bond (at the point of ligation).

The first point is that step (b) of claim 16 imposes no limits on the nature of the bond that is formed, or even the nature of the chemical reaction. In particular, claim 16 does not require that the "thiol" group referred to in the last line of claim 16 react with the thioester group (also referred to in the last line of the claim).

It is noted that claim 16 requires that the peptide segment which bears the thioester group must react with a peptide that itself contains a thiol group. This particular condition is met. As is evident, a review of col 6, line 47+, col 8, line 42+ shows that there is one peptide fragment bearing a thioester group, and another peptide fragment which contains a

cysteine residue. Kent does raise the possibility (col 8, line 60+) of protecting the cysteine sulfhydryl group. For the chemist who has made the decision to protect the cysteine sulfhydryl group, the resulting peptide would still "contain a thiol-containing moiety". The argument could stop there and be sufficient. In addition, however, Kent discloses (col 8, line 63+) that protection of the cysteine sulfhydryl group is not necessary under the reaction conditions.

Thus, the claims are rendered obvious.

✧

Claims 16, 39, 40, 42, 43 are rejected under 35 U.S.C. §103 as being unpatentable over Aimoto (USP 6,277,958).

Aimoto discloses a method of peptide synthesis in which amino acids are added sequentially to a growing peptide chain, which peptide bears a C-terminal thioester group. For example, the following peptide was prepared (col 11, line 40+):

Thr-Pro-Asp-Cys(Acm)-Val-Thr-Gly-Lys-Val-Glu-Tyr-Thr-Lys-Tyr-Asn-Asp-Asp-Asp-Thr-Phe-Thr-Val-Lys-Val-Gly-S-$C(CH_3)_2$-CH_2 -$CONH_2$

One of the intermediate peptides was obtained by condensing the (partially) protected amino acid Fmoc-Cys(Acm) with the following peptide:

Val-Thr-Gly-Lys-Val-Glu-Tyr-Thr-Lys-Tyr-Asn-Asp-Asp-Asp-Thr-Phe-Thr-Val-Lys-Val-Gly-S-$C(CH_3)_2$-CH_2 –CONH-Resin

Thus, in this process, the cysteine was "labeled" with the Acm protecting group, thereby meeting the requirement of claim 16, step (a). The amino acid Fmoc-Cys(Acm) is therefore a labeled molecule which "contains a thiol-containing moiety". This protected amino acid was then "ligated" to a peptide bearing a thioester group. Of course, reaction between the thiol-containing moiety and the thioester group does not occur, but as it happens, claim 16 does not require such.

Thus, the claims are rendered obvious.

✹

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber, can be reached at 571-272-0925. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

DAVID LUKTON
PATENT EXAMINER
GROUP 1800